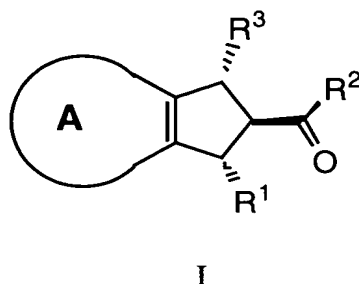
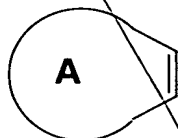


## WHAT IS CLAIMED IS:

1. A process for preparing a compound of Formula I,



wherein:



represents:

- (a) 5- or 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and 1 to 3 heteroatoms selected from O, N and S, and the heterocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH,  $\text{CO}_2\text{R}^4$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ ;
- (b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, and the carbocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH,  $\text{CO}_2\text{R}^4$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ ; or
- (c) aryl, wherein aryl is defined as phenyl or naphthyl, which is optionally substituted with one to three substituents selected from the group consisting of: OH,  $\text{CO}_2\text{R}^4$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ , or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one to three heteroatoms selected from O, N, and S, this ring being optionally substituted on carbon or nitrogen

with one to three substituents selected from the group consisting of: H, OH,  $\text{CO}_2\text{R}^6$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{N}(\text{R}^7)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ ;

and wherein  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ , or  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$  substituent of aryl is further optionally substituted with one to three substituents

selected from the group consisting of: OH,  $\text{CO}_2\text{R}^4$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{OCPh}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ ;

$\text{R}^1$  is:

- (a)  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ , or  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ;
- (b) aryl, wherein aryl as defined above, or
- (c) heteroaryl, wherein heteroaryl is defined as a 5- or 6-membered aromatic ring containing one to three heteroatoms selected from O, N and S, and is optionally substituted with one to three substituents selected from the group consisting of: OH,  $\text{CO}_2\text{R}^4$ , Br, Cl, F, I,  $\text{CF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $(\text{C}_1\text{-C}_8)\text{-alkoxy}$ ,  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,  $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ ,  $\text{CO}(\text{CH}_2)_n\text{CH}_3$ , and  $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$ ;

$\text{R}^2$  is:  $\text{OR}^4$  or  $\text{N}(\text{R}^5)_2$ ;

$\text{R}^3$  is:

- (a)  $(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,
- (b)  $(\text{C}_2\text{-C}_8)\text{-alkenyl}$ ,
- (c)  $(\text{C}_2\text{-C}_8)\text{-alkynyl}$ ,
- (d)  $(\text{C}_3\text{-C}_7)\text{-cycloalkyl}$ ,
- (e) aryl, wherein aryl as defined above,
- (f) heteroaryl, wherein heteroaryl as defined above,
- (g)  $-\text{CHO}$ ,
- (h)  $-\text{CO}(\text{C}_1\text{-C}_8)\text{-alkyl}$ ,
- (i)  $-\text{CO}\text{-aryl}$ ,

- (j) -CO-heteroaryl, or  
 (k) -CO<sub>2</sub>R<sup>4</sup>;

n is: 0 to 5;

t is: 0, 1 or 2;

R<sup>4</sup> is: H, or (C<sub>1</sub>-C<sub>8</sub>)-alkyl;

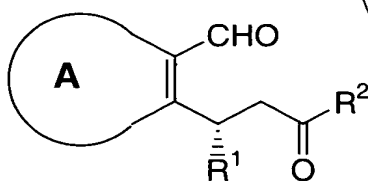
R<sup>5</sup> is: H, (C<sub>1</sub>-C<sub>8</sub>)-alkyl or aryl, wherein aryl as defined above;

R<sup>6</sup> is: H, (C<sub>1</sub>-C<sub>8</sub>)-alkyl or aryl, wherein aryl as defined above; and

R<sup>7</sup> is: H, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, aryl or alkyl, wherein aryl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO<sub>2</sub>R<sup>4</sup>, Br, Cl, F, I, CF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>, (C<sub>1</sub>-C<sub>8</sub>)-alkoxy, (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>2</sub>-C<sub>8</sub>)-alkenyl, (C<sub>2</sub>-C<sub>8</sub>)-alkynyl, (C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, CO(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, and CO(CH<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>, or when two R<sup>7</sup> substituents are on the same nitrogen they can join to form a ring of 3 to 6 atoms;

comprising the steps of:

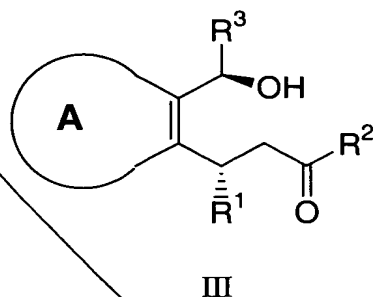
- (1) reacting a Grignard reagent with a conjugate adduct compound of Formula II,



II

in the presence of a first aprotic solvent and optionally an additive at a temperature range of about -80°C to about 30°C to give a Grignard addition product of Formula III; and

Sub  
A'  
cont.



(2) adding phosphoramidate reagent to a mixture of the Grignard addition product of Formula III, a second aprotic solvent and a base at a temperature range of about -80°C to about 30°C to produce the desired compound of Formula I.

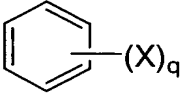
2. The process of Claim 1, wherein the first or second aprotic solvent is selected from the group consisting of tetrahydrofuran, acetonitrile, dimethylacetamide, dimethylformamide, diethyl ether, N-methylpyrrolidinone, dichloromethane, methyl t-butyl ether, toluene, benzene, hexane, pentane, dioxane, and a mixture thereof.

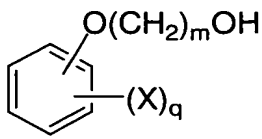
3. The process of Claim 2, wherein the first aprotic solvent is a 1:1 mixture of N-methylpyrrolidinone and tetrahydrofuran at temperature range of about -40°C to about -50°C or N-methylpyrrolidinone at temperature range of about -20°C to about -10°C.

4. The process of Claim 3, wherein the additive is selected from the group consisting of  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ ,  $\text{LiBr}$ ,  $\text{BF}_3 \cdot \text{ET}_2\text{O}$ ,  $\text{ArLi}$ , and DMPU.

5. The process of Claim 4, wherein the Grignard reagent is  $\text{ArMgX}$ , which is prepared from  $\text{ArX}$  and  $\text{Mg}$ .

6. The process of Claim 5, wherein  $\text{ArX}$  is prepared by the following steps:

(a) reacting  with  $\text{HO}(\text{CH}_2)_m\text{OH}$  in the presence of a

base to give , wherein q is 1 to 5, m is 2, 3, or 4, and X is Br, Cl, F, or I;

5 (b) halogenating -O(CH<sub>2</sub>)<sub>m</sub>OH substituent of the benzene to produce the benzene with -O(CH<sub>2</sub>)<sub>m</sub>X substituent in the presence of an aprotic solvent, water, and halogenating agent at a temperature range of about 0°C to about 90°C; and

10 (c) cyclizing the compound produced in step (b) in the presence of alkyl lithium or aryl lithium to give ArX.

7. The process of Claim 6, wherein the ArX is 6-bromo-2,3-dihydrobenzofuran.

15 8. The process of Claim 7, wherein the temperature range in step (1) is about -40°C to about -50°C.

20 9. The process of Claim 8, wherein the phosphoramidate reagent is N,N,N,N-tetra(C<sub>1</sub>-C<sub>6</sub>)-alkylphosphorodiamidic halide or N,N,N,N-tetraarylphosphorodiamidic halide.

10. The process of Claim 9, wherein the phosphoramidate reagent is N,N,N,N-tetramethylphosphorodiamidic chloride,  
N,N,N,N-tetramethylphosphorodiamidic bromide,  
25 N,N,N,N-tetraethylphosphorodiamidic chloride,  
N,N,N,N-tetraethylphosphorodiamidic bromide,  
N,N,N,N-tetraisopropylphosphorodiamidic chloride,  
N,N,N,N-tetraisopropylphosphorodiamidic bromide,  
N,N,N,N-tetraphenylphosphorodiamidic chloride, or  
30 N,N,N,N-tetraphenylphosphorodiamidic bromide.

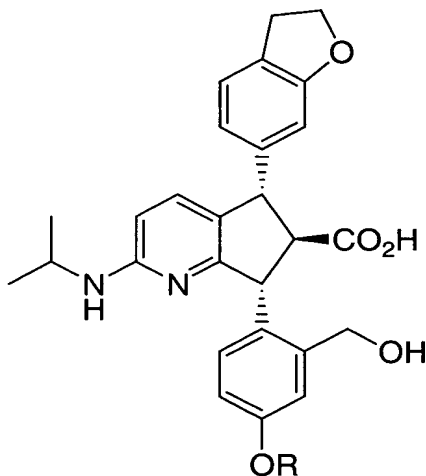
11. The process of Claim 10, wherein the base is selected from the group consisting of n-butyl lithium, phenyl lithium, potassium *tert*-butoxide, sodium hydride, lithium diisopropylamide, lithium diethylamide, lithium dimethylamide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide.

12. The process of Claim 11, wherein the base is sodium hexamethyldisilazide which is present in amounts between about 1 equivalents and about 6 equivalents relative to the amount of the phosphoramidate reagent.

13. The process of Claim 12, wherein the second aprotic solvent is THF or a mixture of THF and toluene.

14. The process of Claim 13, wherein the temperature range in step (2) is about -20°C to about 25°C.

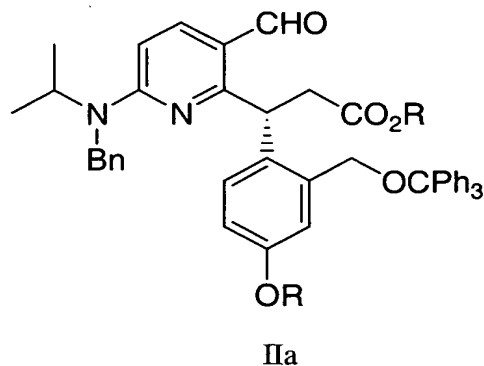
15. A process for preparing a compound of Formula Ia:



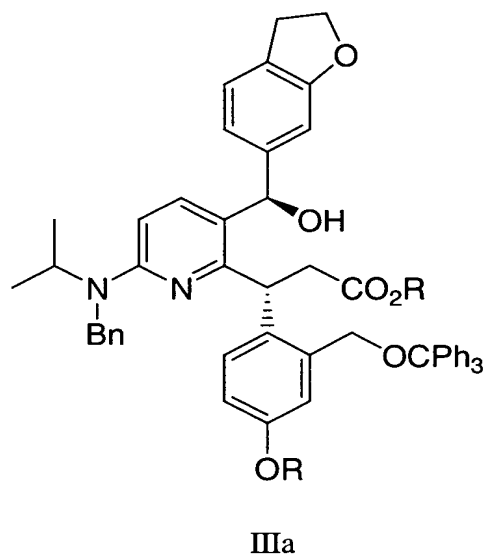
Ia

wherein R is independently H or (C<sub>1</sub>-C<sub>6</sub>)-alkyl comprising the steps of:

(1) reacting ArMgX reagent with a conjugate adduct of Formula IIa,



in the presence of a first aprotic solvent at a temperature range of about -80°C to about 30°C to give a Grignard addition product of Formula IIIa, and



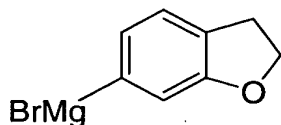
(2) adding phosphoramidate reagent to a mixture of the Grignard addition product of Formula IIIa in a second aprotic solvent and a base at a temperature range of about -80°C to about 30°C to produce the desired compound of Formula Ia.

16. The process of Claim 15, wherein the first or second aprotic solvent is selected from the group consisting of tetrahydrofuran, acetonitrile, dimethylacetamide, dimethylformamide, diethyl ether, N-methylpyrrolidinone, dichloromethane, methyl t-butyl ether, toluene, benzene, hexane, pentane, dioxane, and a mixture thereof.

17. The process of Claim 16, wherein the first aprotic solvent is a 1:1 mixture of N-methylpyrrolidinone and tetrahydrofuran at a temperature range of about -40°C to about -50°C or N-methylpyrrolidinone at temperature range of about -20°C to about -10°C.

5

18. The process of Claim 17, wherein the Grignard reagent is



19. The process of Claim 18, wherein the temperature range in step (1) is about -50°C to about -40°C.

20. The process of Claim 19, wherein the phosphoramidate reagent is N,N,N,N-tetramethylphosphorodiamidic chloride, N,N,N,N-tetramethylphosphorodiamidic bromide, N,N,N,N-tetraethylphosphorodiamidic chloride, N,N,N,N-tetraethylphosphorodiamidic bromide, N,N,N,N-tetraisopropylphosphorodiamidic chloride, N,N,N,N-tetraisopropylphosphorodiamidic bromide, N,N,N,N-tetraphenylphosphorodiamidic chloride, or N,N,N,N-tetraphenylphosphorodiamidic bromide.

21. The process of Claim 20, wherein the base is selected from the group consisting of n-butyl lithium, phenyl lithium, potassium *tert*-butoxide, sodium hydride, lithium diisopropylamide, lithium diethylamide, lithium dimethylamide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide.

22. The process of Claim 21, wherein the base is sodium hexamethyldisilazide which is present in amounts between about 1 equivalent and about 6 equivalents relative to the amount of the phosphoramidate reagent.

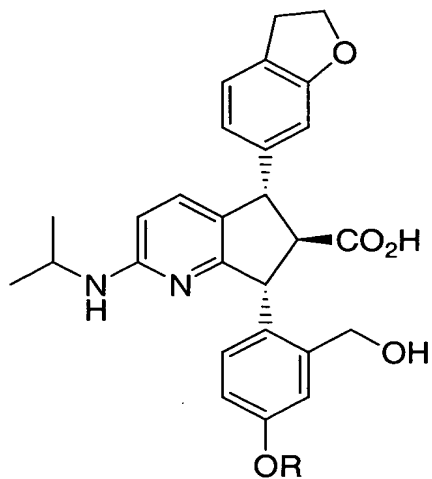
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23. The process of Claim 22, wherein the second aprotic solvent is THF or a mixture of THF and toluene.



24. The process of Claim 23, wherein the temperature range in step (2) is about -20°C to about 25°C.

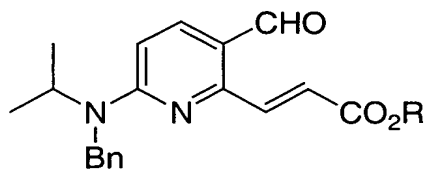
5 25. A process for preparing a compound of Formula Ia,



Ia

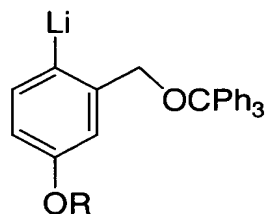
10 wherein R is independently H or (C<sub>1</sub>-C<sub>6</sub>)-alkyl comprising the steps of:

(1) reacting an  $\alpha,\beta$ -unsaturated ester



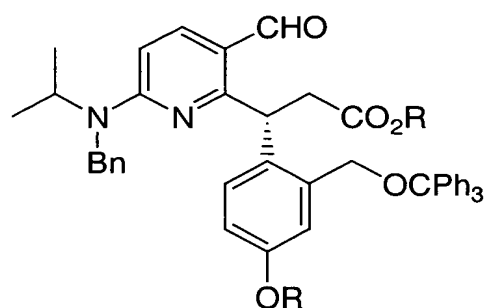
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with a chiral auxiliary (S,S)-pseudoephedrine followed by treatment with an aryllithium compound



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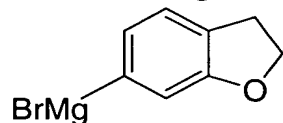
in toluene or tetrahydrofuran or a mixture thereof at a temperature range of about -80°C to about 0°C to give a conjugate adduct of Formula IIa,



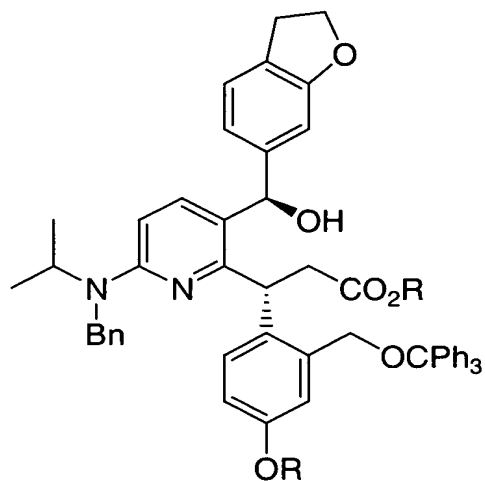
IIa

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(2) reacting the conjugate adduct of Formula IIa with

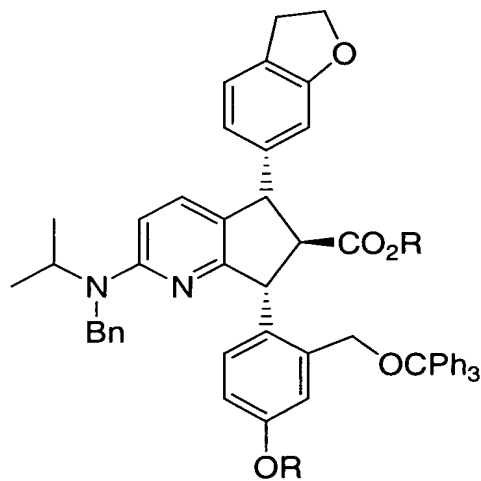


at a temperature range of about -80°C to about 30°C to give a Grignard addition product of Formula IIIa,



IIIa

- (3) adding phosphoramidate reagent to a mixture of the Grignard addition product of Formula IIIa in the presence of tetrahydrofuran or a mixture of tetrahydrofuran and toluene, and a base at a temperature range of about -80°C to about 30°C to produce a cyclized compound of Formula IV, and



IV

- (4) removing protecting groups on the cyclized compound of Formula IV to give the desired compound of Formula Ia.

26. The process of Claim 25, wherein the phosphoramidate reagent is N,N,N,N-tetramethylphosphorodiamidic chloride, N,N,N,N-tetramethylphosphorodiamidic bromide, N,N,N,N-tetraethylphosphorodiamidic chloride, N,N,N,N-tetraethylphosphorodiamidic bromide, N,N,N,N-tetraisopropylphosphorodiamidic chloride, N,N,N,N-tetraisopropylphosphorodiamidic bromide, N,N,N,N-tetraphenylphosphorodiamidic chloride, or N,N,N,N-tetraphenylphosphorodiamidic bromide.
27. The process of Claim 26, wherein the base is sodium hexamethyldisilazide which is present in amounts between about 1 equivalent and about 6 equivalents relative to the amount of the phosphoramidate reagent.
28. The process of Claim 27, which further comprises the steps of:
- deprotecting the cyclized compound of Formula IV by removing protecting groups with acid at a temperature range of about 0°C to about 25°C;
  - crystallizing the deprotected compound as benzylamine salt; and
  - hydrogenating the deprotected compound in the presence of a hydrogenation catalyst and a protic solvent at a temperature range of about 25°C to about 40°C.
29. The process of Claim 28, wherein the hydrogenation catalyst is Pd/C.
30. The process of Claim 29, wherein the protic solvent is selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>) alcohol, H<sub>2</sub>O and a mixture thereof.